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BOTANICALS

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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857
Re: Docket No. 00D-1392

Please consider the following comments and suggestions related to the "Guidance for Industry, Botanical Drug Products, Draft Guidance" published in the Federal Register of August 11, 2000.

In Section V., the guidance referred to the three to five year regulatory exclusivity following NDA approval. This raises the issue of the FDA position on ANDAs for botanical drug products. The difficulty of demonstrating exact bioequivalence to support an ANDA for such a product is generally recognized. Equivalence based on chromatographic and/or chemical assays would be very complex equivalence based on bioassays would be variable and/or assay method dependent. Therefore, it is generally assumed that an ANDA would not be acceptable for a botanical drug. This issue should be addressed specifically. If an ANDA is acceptable, the bioequivalence requirements for a botanical product derived from a single plant and for a botanical product derived from multiple plants should be specified.

Chemistry, Manufacturing and Control Issues:

Several sections of the Guidance specify a bioassay requirement at several different levels in the manufacturing process. Section IX – INDs for Phase 3 Clinical Studies of all Botanical Products B.*1*.c. specifies a biological assay as a *quality control test* for the botanical drug product. We believe additional thought should be given to this requirement and that it should be removed or made optional rather than mandatory for the following reasons. As a quality control release requirement, it is an expensive and variable requirement for repeated use at multiple stages in the manufacturing process as well as on every batch of the botanical drug product. Animal or tissue based bioassays are too variable to be meaningful and enzyme based bioassays (high throughput type models) which are mechanism specific and therefore too narrow to be practical for use with a multiple ingredient mixture. It is suspected that this requirement is a result of the use of bioassays by some sponsors to differentiate their specific products. We submit that a bioassay requirement is not necessary or even particularly useful for adequate characterization of botanical drug products and merely adds unwarranted expense to the manufacturing process.

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If the Agency determines that this requirement must be retained, qualifying language should be included to allow adequate flexibility in choice of assay and range of variability to make them practical for routine use in manufacturing commercial products.

This same section further specifies two chemical identification tests and a bioassay for the QC release of Botanical Drug Products (BDP). The need for this should be explained more fully, with an emphasis on the rationale for requiring both the spectroscopic or chromatographic fingerprints and the chemical identification of the active constituents or markets. As outlined in the paragraph above, these chemical identification tests should be sufficient to characterize a botanical drug product without the need for a biological assay.

Section IX. – INDs for Phase 3 Clinical Studies of all Botanical Products B.*1*.g. specifies that Stability-indicating assay of BDS or BDP generally should not be based entirely on the assay of the active constituents, characteristic markers, or biological assay, because degradants formed from other constituents, during storage, should also be controlled. Although the intent of this section is desirable in principle, and is feasible for single active ingredient drug products, it is prohibitively expensive and therefore an unrealistic requirement for botanical drug products. In some cases it may not be possible. The stability of mixtures derived from plant sources should be of concern and should be monitored, however, these requirements should be qualified to allow flexibility based on what is economically practical and technically possible and whether the degradants pose a real risk to product users. Alternatively, public safety could be assured by making provisions for the use of special packaging and/or storage conditions if necessary in situations where such stability indicating assay procedures may be technically impractical and/or overly expensive.

There seem to be inconsistencies between ICH Consensus Guideline on GMPs for Active Pharmaceutical Ingredients and the FDA Botanical Guideline regarding compliance with GMPs for the manufacture of the botanical extract. These inconsistencies should be evaluated and reconciled to the extent possible when comparing the two processes.

Preclinical Safety Assessment (Including Pre-NDA):

The first paragraph in Section IX.C. states, *"To support safety for expanded clinical studies or to support marketing approval of a botanical drug product, toxicity data from standard toxicology studies in animals may be needed. .....the timing of these animal studies in relation to concurrent clinical trials and other requirements for preclinical animal studies can vary."*

We urge the Agency to carefully consider the appropriateness of using animal data to predict human safety for products with a significant history of human use. Although some provision is made for considering human use data to support safety, we are concerned that this requirement may have been included because of familiarity rather than appropriateness. This, coupled with the absence of personnel trained in the evaluation of epidemiological data at the Agency may have worked against consideration of previous human use experience, even when direct human data is available. This concern will also be discussed more generally below. It should be noted that animal safety testing (animal toxicology) was developed to extrapolate animal toxicity to humans for drugs to which humans had not been previously exposed. The appropriateness of using animal safety studies as the indicator of choice for predicting the safety of products with a history of human use should be seriously questioned.

We submit that previous safe human exposure should be used as the primary indicator of human safety where available, with scientific data from animal testing being required only when relevant human use data is unavailable. This preference should be clearly stated in the Botanical Drug Guidance. At a minimum, it should be clearly stated that the Agency would consider such data for botanical drugs with a history of human use in lieu of animal safety data whenever possible instead of reliance on modifiers such as "may" and "might". We recognize that this will require adding additional personnel trained in the use of epidemiological procedures to analyze human use data and submit that this would be a sound investment for the Agency.

General Issues:

The Guidance for Industry for Botanical Drugs is a significant step forward, and we commend the FDA for issuing it, but we respectfully remind the Agency that the document continues to essentially outline the requirements for a new chemical entity with an overlay of requirements thought to be more appropriate for botanical drug products. This is not surprising, since all or nearly all of the reviewers at the Agency were educated and trained during the last 50 years, in an era in which botanical drugs were not a part of the regulatory environment in the United States. It is human nature to view issues within a context of "the way things have always been done". The current "institutional memory" of the agency developed and most of the current implementing regulations for the IND/NDA process were also written during this same 50-year period, which tends to reinforce this tendency. We urge the Agency to serious consider the most appropriate methodology when considering botanical drugs with a previous history of human use.

We understand and appreciate that the primary charge of the Agency is to protect the public health and insure that all new drug products are safe and efficacious as labeled. We also recognize that INDs and NDAs have historically been evaluated on a case-by-case-basis. Within this context, we urge the Agency to re-word the Guidance Document to clearly indicate that Sponsors will be allowed to demonstrate safety and efficacy by the most appropriate means possible when pursuing the IND/NDA pathway. Doing so would encourage Sponsors to develop safe and effective products for sale at a reasonable cost to the consumer. It will permit the Agency to maintain the public safety, increase the quality of botanical products available and health care practitioners, enhance public confidence and encourage reasonable pricing for botanical drugs.

Sincerely,

Floyd E. Leaders, Jr., Ph.D.
Chairman and CEO